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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,696	12/03/2003	Chaitan Khosla	300622000508	8649

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EXAMINER	
NASHED, NASHAAT T	

ART UNIT	PAPER NUMBER
1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,696	KHOSLA ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,10-13 and 31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,10-13 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/1/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 1, 2007 has been entered.

The application is amended as requested in the communication filed August 1, 2007. Accordingly, claims 1 and 7 are amended, new claim 31 is added, and claims 8 and 9 are have been canceled.

Claims 1-5, 7, 10-13, and 31 are under consideration in this Office action.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The phrases "a nucleotide sequence consisting essentially of a nucleotide sequence encoding an acyltransferse (AT) domain" and "a nucleotide sequence consisting essentially of second AT domain" in claim 1 are not found any where in the specification or the claims as originally filed. The word "essentially" expands the scope of the teaching of the specification to include additional nucleic acid elements to be added to the AT domain, which is not taught in the specification. The deletion of the phrase "consisting essentially of" from the claim would vacate this rejection. Claims 2-5 and 31 are include in this rejection because they are dependent on claim 1 and do not cure its deficiencies.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-5 and 31 are rejected under 35 U.S.C. § 102(b) as being anticipated by Katz et al. (Katz, WO 93/13663) for the reasons set forth in the prior Office actions mailed 5/10/06 and 2/1/07.

Claims 1-5 and 31 are rejected under 35 U.S.C. § 102(e) as being anticipated by U. S. P 5,824,513 ('513, IDS reference number 5) for the reasons set forth in the prior Office actions mailed 5/10/06 and 2/1/07.

In response to the above rejection, applicants appear to agree that the cited references above appear to be the same. They continue to argue that there is no place in the application wherein the substitution of an AT domain by another is described.

Applicants' arguments filed 8/1/07 have been fully considered, but they are found unpersuasive. The references teach specifically the substitution of the AT domain in a PKS to produce novel polyketides and exemplified the substitution of other domains using homologues recombination. See above and the prior Office actions. Also, they teach the excision of a domain using restriction enzymes and ligation of said domain to other nucleic acids. The substitution of one AT domain by another is fully enabled in the specification of both document because cutting an pasting fragments of nucleic acid were well-known in the prior art at the time of invention, i.e., the time of publication of '663 document and filing the U. S. patent application that was matured to the '513 patent. Also, introducing restriction sites by PCR were well known in the prior art at said time of invention (new claim 31).

Thus, the prior art describe and taught the claimed invention and therefor, the claims remain rejected.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7, 10-13, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over by Katz (WO 93/13663) or U. S. P 5,824,513 ('513, IDS reference number 5) or in view of the state of the art as exemplified by Kao *et al.* (IDS reference: Science 1994, 265, 509-512).

Katz teach a method for obtaining novel polyketides by introducing specific changes in the DNA encoding the biosynthetic pathway of a polyketide, the summary of

invention on page 2, the DNA sequence for the *ery* gene cluster and the amino acid sequences of the three open reading frame encoded thereby, see Figure 2, and exemplify the changes in the *ery* gene cluster (also known as DEBS). Figure 1 describes the various enzymatic activities in each open reading frame. Also, they teach that the extender unit employed at each condensation is specified by the acyltransferase function determined by each module, see page 6, lines 26-29, and the production of polyketide in microorganisms producing polyketide such as *Saccharapolyspora erythrea*, *Streptomyces antibioticusl*, *S. hygroscopicus* and *S. venezuelae* among others, see page 4, last paragraph. The method taught by Katz encompasses transforming a polyketide producing microorganism with the modified nucleic acid and culturing the microorganism and harvesting the product polyketide. The instant claims are directed to a method for modifying the acyltransferase activity in a modular polyketide synthase by another acyltransferase activity, a modification described by Katz as type III changes using restriction enzymes, see page 7, lines 12-18; and examples 7, 11, 15, 19, and 24. Specifically, Katz teach the replacement of the acyltransferase in any module by another acyltransferase from the same gene cluster or different gene cluster such as that of *S. venezuelae* wold be expected to produce predictable change in the structure of polyketides, see page 35, line 17-36. Also, claim 16 of Katz is drawn to a method for directing the biosynthesis of specific polyketide by genetic manipulation, which includes the replacement of a nucleic acid encoding an acyltransferase activity by another nucleic acid encoding an acyltransferase activity with different specificity. In addition, Katz teach that the method is applicable to any gene cluster including those encoding the biosynthetic pathway of rapamycin (produced by *S. hygroscopicus*), avermectin, FK-506, and tylosin, see page 36, lines 10-20.

The '513 patent appear to be identical to Katz (WO 93/13663). It teaches a method for obtaining novel polyketide by introducing specific changes in the DNA encoding the biosynthetic pathway of a polyketide, the summary of invention, the paragraph bridging columns 1 and 2, the DNA sequence for the *ery* gene cluster and the amino acid sequences of the three open reading frame encoded thereby, see Figure 2, and exemplify the changes in the *ery* gene cluster (also known as DEBS). Figure 1 describes the various enzymatic activities in each open reading frame. Also, it teaches that the extender unit employed at each condensation is specified by the acyltransferase function determined by each module, see column 4, lines 52-56, and the production of polyketide in microorganisms producing polyketide such as *Saccharapolyspora erythrea*, *Streptomyces antibioticusl*, *S. hygroscopicus* and *S. venezuelae* among others, see column 3, lines 30-50. The method taught in the 513 patent encompasses transforming a polyketide producing microorganism with the modified nucleic acid and culturing the microorganism and harvesting the product polyketide. The instant claims are directed to a method for modifying the acyltransferase activity in a modular polyketide synthase by another acyltransferase activity, a modification described in the patent as type III changes, see column 4, lines 16-21. Specifically, the '513 teaches the replacement of the acyltransferase in any module by another acyltransferase from the same gene cluster or different gene cluster

such as that of *S. venezuelae* would be expected to produce predictable structure change in the polyketide, see starting in column 23, line 31 through line 5 of column 24. Also, claim 1 in the '513 patent is drawn to a method for directing the biosynthesis of specific polyketide by genetic manipulation which includes the replacement of a nucleic acid encoding an acyltransferase activity by another nucleic acid encoding an acyltransferase activity with different specificity, see claim 1 (c)(vi). In addition, the '513 patent teaches that the method is applicable to any gene cluster including those encoding the biosynthetic pathway of rapamycin, avermectin, FK-506, and tylosin, see column 23, line 47 through column 24, line 32. Finally, they teach the use of restriction enzymes to carry out the modification of the nucleic acid *in vivo* and the use, see examples, which describe the various methodology of substituting domains combinations of plasmids and restriction enzymes.

Kao *et al.* teach a novel vectors and a method of constructing hybride polyketide synthase for the production of novel polyketides. See the abstract. The method summarized in Figure 2 in which a recipient plasmid such as pCK5 comprising the entire PKS gene cluster and selection marker and a donor plasmid comprising the desired modified nucleic acid sequence attached to flaking sequences at the 5'- and 3'-end that would allow homologues recombination with the recipient plasmid, and selection marker. Replication of the temperature sensitive plasmid occurs at 30 degrees and arrested at 44 degrees. The plasmids and vectors taught by Kao *et al.* are designed, in particular, to manipulate the large polyketide synthase gene clusters and to obtain modified gene clusters for the biosynthesis of novel polyketides. See column 3 at page 507.

Both the '633 document and '513 document provide on of ordinary skill in the art to identify novel polyketides, and teach that the substitution of the AT domain in a gene cluster by another having different substrate specificity leads to the production of novel polyketides. Also, Kao *et al.* teach that polyketides have antibiotic, anti cancer, and immunosuppressant activities and that new gene clusters can be engineered. See page 509, column 1, after the abstract, and column 2. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to construct polyketide synthase in which one or more of the AT domain is substituted by another having different substrate specificity from the same or different gene cluster. The substitution as the term means cutting one domain and replace by another. Thus, one of ordinary skill in the art would have generated specific restriction sites at the boundaries of the AT domain by well known methods in the art, excise the first AT domain with the desired activity using restriction enzymes, excise the undesired AT domain from the desired gene cluster using restriction enzymes, and pasting the first desired AT domain to the gene cluster by well known methods in the art (claim 1). Both the '633 and '513 documents teach that the source of the AT domain or gene cluster can be any one of erythromycin, rapamycin, FK-506, and tylosin, which were all known in the prior art at the time of invention (claims 2-5). Applicant should note that insertion of a restriction site by PCR into a gene is a standard and well-known method in the art (claim 31).

Alternatively, the ordinary skill in the art would have been motivated at the time of invention to use the method taught by Kao *et al.* to construct the modified gene cluster. Thus, it would have been obvious at the time of invention to construct a recipient plasmid comprising the unmodified gene cluster and a temperature sensitive donor plasmid comprising the desired AT domain flanked by native sequences from said gene cluster, wherein each plasmids comprise different selectable markers and carry out the modification method as taught by Kao *et al.* (claims 7 and 10-13). Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen K. Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nashed/
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Art Unit 1656